CLAIMS

What is claimed is:

1. An isolated human PAB II gene comprising a polymorphic GCG repeat in exon I thereof wherein an allelic variant of said GCG repeat is indicative of a disease associated with protein accumulation in a cell nucleus, swallowing difficulty, and/or ptosis in a human patient.

2. The gene of claim 1, wherein said polymorphic GCG repeat has the sequence

ATG $(GCG)_{6+n}$ GCA,

wherein n is selected from 1 to 7.

3. The gene of claim 2, wherein n is selected from 2 to 7, and wherein said allelic variant is associated with an increased severity of the disease.

4. The gene of claim 3, wherein a phenotype associated with said allelic variant is dominant.

5. The gene of claim 2, wherein a first allele of said GCG repeat has an n which is equal to 1.

6. The gene of claim 5, wherein a second allele of said GCG repeat has an n selected from 2 to 7, and wherein said first allele is a modulator of the severity of the phenotype associated with said second allele.

7. The gene of claim 1, wherein said human patient is homozygous for said polymorphic GCG repeat.

8. The gene of claim 1, wherein said human patient is heterozygous for said polymorphic GCG repeat.

9. A nucleic acid sequence comprising a polymorphic GCG repeat of exon I of a human PAB II gene, wherein an allelic variant of said GCG repeat in a patient's human PAB II gene is indicative of a disease associated with protein accumulation in a cell nucleus, swallowing difficulty, and/or ptosis in said human patient.

10. The nucleic acid sequence of claim 9, wherein said polymorphic GCG repeat has the sequence

ATG $(GCG)_{6+n}$ GCA,

wherein n is selected from 1 to 7.

11. The nucleic acid sequence of claim 10, wherein n is selected from 2 to 7, and wherein said allelic variant is associated with an increased severity of said disease.

12. The nucleic acid sequence of claim 11, wherein a phenotype associated with said allelic variant is dominant.

13. A method for the diagnosis or prognosis of a disease associated with protein accumulation in a cell nucleus, and/or swallowing difficulty and/or ptosis in a human patient, which comprises:

a) obtaining a nucleic acid sample of said patient; and

b) determining allelic variants of a GCG repeat in exon I of the PAB II gene, said GCG repeat having the sequence

ATG $(GCG)_{6+n}$ GCA,

wherein n is selected from 0 to 7, and

whereby at least one allele of said GCG repeat having an n equal to 1 to 7, is indicative of a disease related with said protein accumulation in said nucleus, and/or a swallowing difficulty and/or ptosis in said patient.

14. The method of claim 13, wherein n is selected from 2 to 7, and wherein said allelic variant is associated with an increased severity of said disease.

15. The method of claim 14, wherein said phenotype associated with said allelic variant is dominant.

16. The method of claim 13, wherein a first allele of said GCG repeat has an n which is equal to 1.

17. The method of claim 16, wherein a second allele of said GCG repeat has an n selected from 2 to 7, and wherein said first allele is a modulator of the severity of the phenotype associated with said second allele.

18. The method of claim 13, wherein said disease is oculopharyngeal muscular dystrophy.

19. A non-human transgenic animal whose germ cells and somatic cells are modified to express at least one allelic variant of a polymorphic GCG repeat in exon I of the PAB II gene, and wherein said transgenic animal shows a phenotype of a disease associated with protein accumulation in a cell nucleus, and/or a swallowing difficulty and/or ptosis.

20. The non-human transgenic animal of claim 19, wherein said polymorphic GCG repeat has the sequence

$$ATG\ (GCG)_{6+n}\ GCA,$$

wherein n is selected from 1 to 7.

21. The transgenic animal of claim 19, wherein said animal is a mammal.

22. The transgenic animal of claim 19, wherein said allelic variant of the PAB II gene is a human allelic variant.

23. The transgenic animal of claim 19, having cells which display a protein accumulation in their nucleus.

24. A cell isolated from said non-human transgenic animal according to claim 19.

25. A method for screening and identifying an agent for the prevention and/or treatment of a disease associated with protein accumulation in a cell nucleus and/or a swallowing difficulty, and/or ptosis, said method comprising:

a) exposing the transgenic animal of claim 19 to said agent; and

b) evaluating the prevention and/or treatment of development of said protein accumulation in a cell nucleus and/or a swallowing difficulty, and/or ptosis in said animal exposed to said agent as compared to a control animal not having been exposed to said agent.

26. A method for screening and identifying an agent which modulates protein accumulation in the nucleus of a cell, said method comprising:

a) exposing a cell of claim 24 to said agent; and

b) evaluating said protein accumulation in said nucleus of said exposed cell as compared to a control cell not having been exposed to said agent.

27. The method of claim 25, wherein said protein accumulation is associated with oculopharyngeal muscular dystrophy.

28. A cell which has been modified to express at least one allelic variant of a human polymorphic GCG repeat of exon I of the PAB II gene, wherein said allelic variant is associated with protein accumulation in the nucleus of said cell.

29. The cell of claim 28, wherein said polymorphic GCG repeat has the sequence

$$ATG\ (GCG)_{6+n}\ GCA,$$

wherein n is selected from 1 to 7.

30. The cell of claim 28, wherein said cell is a mammalian cell.

31. An isolated human PAB II gene comprising a polymorphic GCG repeat in exon I thereof, wherein said repeat has the sequence ATG $(GCG)_{6+n}$ GCA, wherein n is 0, and wherein said sequence is indicative of a non-disease phenotype associated with protein accumulation in a cell nucleus, swallowing difficulty, and/or ptosis in a human patient.

32. The human PAB II gene of claim 31, wherein said gene is as set forth in SEQ ID NO:3.

33. A method of diagnosing a disease in a human patient associated with a meiotically stable trinucleotide expansion in a coding sequence of a gene comprising:

a) obtaining a nucleic acid sample from said patient;

b) determining whether said gene comprises at least one trinucleotide expansion, wherein the determination of one trinucleotide expansion in said coding region of said gene is indicative of a disease condition in said patient.

34. The method of claim 33, wherein said trinucleotide expansion has the sequence

ATG(GCG)$_{6+n}$GCA,

wherein n is 1 to 7.

35. The method of claim 33, wherein said disease is associated with protein accumulation in a cell nucleus and/or a swallowing difficulty and/or ptosis.

36. The method of claim 33, wherein said disease is oculopharyngeal muscular dystrophy.